UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C. 20460

OFFICE OF
THE ADMINISTRATOR
EPA SCIENCE ADVISORY BOARD

October 1, 2003

The Honorable Marianne L. Horinko
Acting Administrator
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, N.W.
Washington, D.C. 20460

Subject: Review of the draft Supplemental Guidance For Assessing Cancer Susceptibility From Early-Life Exposure To Carcinogens

Dear Acting Administrator Horinko:

On May 12-14, 2003, the Supplemental Guidance For Assessing Cancer Susceptibility (SGACS) Review Panel of the U.S. EPA Science Advisory Board's (SAB) Environmental Health Committee (EHC) along with members of the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) and Children's Health Protection Advisory Committee (CHPAC) met to review the Agency's draft Supplemental Guidance For Assessing Cancer Susceptibility From Early-Life Exposure To Carcinogens document (Supplemental Guidance). The Agency requested that the SAB conduct a review of the draft document entitled "Supplemental Guidance for Assessing Cancer Susceptibility from Early-Life Exposure to Carcinogens" in an expedited manner and utilize the expertise of two other EPA advisory committees, the SAP and CHPAC. By including members of these three EPA advisory bodies in the review of this guidance, the requesting office hoped to benefit from their unique expertise in children's risk assessment, and to obtain timely advice.

The SAB has reviewed, fully or in part, EPA's Guidelines for Cancer Risk Assessment that have undergone several revisions. A previous SAB review panel suggested incorporating

age-dependent susceptibility through age-specific adjustment factors for potency or response to exposures when assessing cancer risk.

This current draft Supplemental Guidance represents an attempt by the Agency to be responsive to the recommendations of the previous SAB panel. The draft Supplemental Guidance provides a proposed approach for assessing cancer susceptibility from early-life exposure to carcinogens. The Supplemental Guidance concludes that cancer risks generally were higher from early-life exposure to carcinogengens that act through a mutagenic mode of action than from similar exposure durations later in life. In the absence of chemical specific data on early-life exposure, the Supplemental Guidance provides a default approach to account for differential susceptibility from early-life exposure. Adjustments to the cancer slope factor typically derived from adult exposure will depend on the age group.

- For exposures before 2 years of age, a 10-fold adjustment.
- For exposures between 2 and 15 years of age, a 3-fold adjustment.
- For exposures after 15 years of age, no adjustment.

The SGACS Review Panel appreciates the Agency's consideration of SAB's recommendations and concurs with the overall approach adopted by the Agency of using adjustment factors to account for increased susceptibility due to early-life exposure. The Panel also agrees that the values chosen for the cancer slope adjustment factors in the Supplemental Guidance appear to be reasonable from consideration of the literature. However, the Panel suggests that the Agency improve the statistical analysis of the data and provide a more extensive discussion of how the Agency arrived at the choice of the 10X and 3X adjustment factors. The Panel also suggests that the Agency emphasize that these default adjustment factors would be used only when no chemical-specific data are available to directly assess cancer susceptibility from early-life exposure to a particular carcinogen. The Agency should consider conducting additional research to address this issue directly as discussed in the attached report**.**

In this current review activity, the Agency sought the Science Advisory Board's evaluation of the soundness of the Agency's position that the Agency's analysis and the underlying scientific information support the conclusion that there is greater susceptibility for the development of tumors as a result of exposures in early lifestages as compared with adult exposures to chemicals acting through a mutagenic mode of action. The SGACS review panel was specifically asked to respond to the following charge questions that are divided into two

parts, (1) questions concerning the supplemental guidance for assessing cancer susceptibility from early-life exposure to carcinogens and (2) other questions:

CHARGE QUESTIONS AND PANEL RECOMMENDATIONS:

Questions Concerning The Supplemental Guidance For Assessing Cancer Susceptibility From Early-Life Exposure To Carcinogens

1. Please comment on whether the Agency's analysis as applied to chemicals acting through a mutagenic mode of action is accurate, reliable, unbiased and reproducible. Likewise, please comment on whether the underlying scientific information used to develop the guidance is accurate, reliable, unbiased and reproducible. Are there any key studies that the Agency has overlooked in reaching this conclusion?

   The Panel agrees with the Agency that the science supports the conclusion that early life exposures result in increased susceptibility to carcinogens that act through a mutagenic mode of action compared to adults exposures and notes that a broader look at the scientific literature beyond the studies included in the Supplemental Guidance analysis further strengthens that conclusion.

2. For chemicals acting through non-mutagenic modes of action, the Agency concludes that a range of approaches needs to be developed over time for addressing cancer risks from childhood exposures. Please comment on the Agency's conclusion that the scientific knowledge and data are insufficient at this time to develop generic guidance on how to address these chemicals and that a case-by-case approach is more suitable. Is the SAB aware of any additional data for chemicals acting through non-mutagenic modes of action relevant to possible early lifestage sensitivity?

   The Panel notes that for certain groups of non-mutagenic chemicals (e.g., estrogen receptor agonist/antagonist) there is enough evidence supporting increased susceptibility to cancer with early life exposure and suggests that the Agency include a discussion of these agents in the draft Supplemental Guidance. These chemicals serve as important

examples in support of applying a default factor to non-mutagenic carcinogens when the mode of action is unknown. Non-mutagenic carcinogens with known mode of action should be assessed on a case-by-case basis as suggested by the Agency.

3. Assuming that it is appropriate to conclude that there is differential lifestage susceptibility to chemicals acting through a mutagenic mode of action, the Agency's guidance uses a default approach that adjusts cancer slope factors (typically from conventional animal bioassays and/or epidemiologic studies of adult exposure) to address the impact of early lifestage exposure. Please comment on whether the approach is justified by the available data? Can the SAB suggest other approaches that might be equal or more appropriate?

   The Panel supports the use of slope factor adjustments in developing defaultapproaches. Application of an adjustment to the adult cancer slope factor seems to be the most transparent and practical approach for risk assessment.

4. When considering differential susceptibility, the Agency's guidance separates the potential susceptible period into two age groups, 0 - 2 years and 2 - 15 years. These groupings were based on biological considerations rather than exposure considerations. The first grouping, 0 - 2 years of age, is meant to encompass a period of rapid development and the second grouping, 2 - 15 years of age, was selected to extend through middle adolescence approximately following the period of rapid developmental changes during puberty. Please comment on the scientific rationale that was used to justify these age groupings. Can the SAB suggest other plausible ways to make these groupings?

   The Panel discussed the Agency age groupings used in the adjustment factor development and reviewed age-specific human vulnerabilities and concluded that it would be useful to include an additional age grouping (age 9 –15) to recognize the potentially important vulnerabilities during puberty. Thus four age groupings would be appropriate (0-2, 3-8, 9-15, 15+) to represent critical periods of human growth and development.

5. The guidance provides a quantitative approach to account for the greater susceptibility of early-life exposure to chemicals that act through a mutagenic mode of action. An adjustment factor of 10 is applied to the cancer slope factor (derived from animal or epidemiology studies) for exposures before 2 years of age, a factor of 3 is applied for ages between 2 and 15 years, and no adjustment is applied after the age of 15. Please comment on whether the data and EPA analysis are scientifically sufficient to support these adjustment factors. Are sufficient data, including breadth of chemicals, available to make these determinations?

   The Panel suggests that the Agency consider alternative analyses that might allow them to use more of the available data and directly test hypotheses concerning the appropriateness of the adjustment values for predicting the dose-response from early exposure.

Other Questions

6. The Agency recognizes that consideration of children's risk is a rapidly developing area and, therefore, the Agency intends to issue future guidance that will further refine the present draft guidance and possibly address other modes of action as data become available. The Agency welcomes the SAB's recommendations on other modes of action that may be most fruitful to assess in similar future analyses.

   The Panel recommends that a priority for the near term would be the development of mode of action approaches for endocrine disruptors, beginning with estrogenic agents.

7. The analysis presented in the current Guidance relies on postnatal studies. Can the SAB recommend how to best incorporate data from transplacental or in utero exposure studies into future analyses?

   The Panel cannot recommend at this time a feasible method for incorporating transplacental/in utero exposure data. However, the Panel believes this to be an important issue that requires further research.

8. The Agency welcomes the SAB's recommendations on critical data needs that will facilitate the development of future guidance addressing differential lifestage susceptibility.

The Panel recommends that the Agency work more closely with the research community to encourage the evaluation of early-life stage susceptibilities. For chemical agents that are known to increase cancer risk, carcinogenic potency and the extent of exposure should be used in deciding which chemicals to study first.

Additionally, the Panel suggests that the Agency reconsider limiting the application of adjustment factors only to mutagenic agents and instead apply a default approach to both mutagenic and to non-mutagenic chemicals for which mode of action remains unknown or insufficiently characterized.

In closing, the Panel appreciates the Agency's responsiveness to earlier SAB recommendations that the supplemental guidance for assessing cancer susceptibility from early-life exposure to carcinogens be a stand-alone document. Because many parts of the Cancer Guidelines provide the background for the Supplemental Guidance, issuance of the Supplemental Guidance before the Guidelines could be confusing. The Panel, therefore, encourages the Agency to rapidly finalize the Guidelines, and the Supplemental Guidance soon after, if not concurrently. The Panel wishes to commend the Agency for the hard work reflected in the Supplemental Guidance and looks forward to your response to this report.

Sincerely,

Dr. William Glaze, Chair
EPA Science Advisory Board

Dr. Henry Anderson, Chair
SGACS Review Panel
EPA Science Advisory Board